Nebivolol HCl

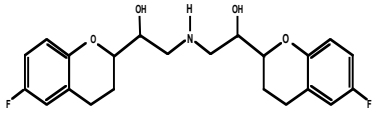
Nebil

2.5mg and 5mg Tablet

Beta-Blocker

DESCRIPTION

Nebivolol (Nebil) is chemically described as (1RS, 1'RS)-1, 1'-[(2RS, 2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]- 2,2'-iminodiethanol hydrochloride. Its molecular formula is $C_{22}H_{25}F_2NO_4$ and its structural formula is:



Nebivolol

FORMULATION

Nebivolol (Nebil) Tablets are available for oral administration as:

1. Nebivolol (Nebil) Tablets 2.5mg
   Each tablet contains:
   Nebivolol HCl equivalent to Nebivolol…2.5mg

2. Nebivolol (Nebil) Tablets 5mg
   Each tablet contains:
   Nebivolol HCl equivalent to Nebivolol…5mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Nebivolol, a racemic mixture of SRRR and RSSS, is a $ß_1$ selective adrenoceptor antagonist whose hemodynamic effects differ from those of classical ß-adrenoceptor antagonist as a result of a vasodilating action. It has mild vasodilating properties attributed to its interaction with the L-arginine/nitric oxide path way, a property not shared by other ß-blockers. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, nebivolol does not demonstrate α_1-adrenergic receptor blockade activity.

Pharmacokinetics

Nebivolol is rapidly absorbed following oral administration. The absorption of nebivolol is not affected by food. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, N-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism and bioavailability and half-life vary widely. In fast metabolisers, the elimination half-life of nebivolol is about 10 hours and of the hydroxy metabolites is about 24 hours. Peak plasma concentration of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.
Nebivolol is about 98% bound to plasma proteins. It is excreted in the urine and feces, almost entirely as metabolites.
The pharmacokinetics of nebivolol are not affected by age. One week after administration, 38% of the dose is excreted in the urine and 48% in the feces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.

Special Populations

Renal insufficiency

The apparent clearance of nebivolol is unchanged following a single 5mg dose of nebivolol in patients with mild renal insufficiency (CrCl 50 to 80mL/min), and it is reduced negligibly in patients with moderate (CrCl 30 to 50mL/min). However it reduced by 53% in patients with severe renal insufficiency (CrCl <30mL/min). The dose of nebivolol should be adjusted in patients with severe renal insufficiency.

Hepatic insufficiency

Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic insufficiency (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic insufficiency.

THERAPEUTIC INDICATIONS

For the treatment of essential hypertension, stable, mild and moderate chronic heart failure in addition to standard therapies in elderly patients ≥ 70 years and may be used alone or in combination with other anti-hypertensive agents.

DOSAGE AND ADMINISTRATION

Hypertension

Adults

The dose is one tablet (5mg) daily, preferably at the same time of the day. Tablets may be taken with or without meals. The initial up titration should be done at 1-2 weekly intervals based on patient tolerability. The maximum recommended dose is 10mg nebivolol once daily. The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks. During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary edema, cardiogenic shock, symptomatic bradycardia or AV block).

Patients with renal insufficiency

In patients with renal insufficiency, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. The upward titration should be performed cautiously.

Patients with hepatic insufficiency

In patients with moderate hepatic insufficiency, the recommended initial dose is 2.5mg once daily. Upward titration should be performed cautiously if needed.

Elderly

In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg.

Chronic heart failure

The treatment of stable chronic heart failure has to be initiated with a gradual up titration of dosage until the optimal individual maintenance dose is reached.
Patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilized during the past two weeks prior to initiation of nebivolol treatment.

ADVERSE EFFECTS

The following adverse reactions occurred:

Hypertension

Common: Headache, dizziness, paresthesia, dyspnea, constipation, nausea, diarrhea, tiredness, edema.

Uncommon: Nightmares, depression, impaired vision, bradycardia, heart failure, slowed AV conduction/AV-block, hypotension, (increase of) intermittent claudication, bronchospasm, dyspepsia, flatulence, vomiting, pruritus, rash, erythematous, impotence.

Rare: Syncope, psoriasis aggravated.

Chronic heart failure

The most commonly reported adverse reactions are bradycardia and dizziness.
The other adverse reactions that occurred are aggravation of cardiac failure, postural hypotension, drug intolerance, first degree atrio-ventricular block, edema of the lower limb.

CONTRAINDICATIONS
Nebivolol is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the components.
- Severe hepatic insufficiency.
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring I.V. inotropic therapy.
- Sick sinus syndrome, including sino-atrial block.
- Second and third degree heart block (without a pacemaker).
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Bradycardia (heart rate < 60bpm prior to start of therapy).
- Hypotension (systolic blood pressure < 90mmHg).
- Severe peripheral circulatory disturbances.

PRECAUTIONS
Anesthesia
Continuation of β–blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.
Caution should be observed with certain anesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiac Failure
In patients who have compensated congestive heart failure, nebivolol should be administered cautiously. If heart failure worsens, discontinuation of nebivolol should be considered.

Metabolic/Endocrinological
Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycemia (tachycardia, palpitations). β-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

Abrupt Cessation of Therapy
The treatment with nebivolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly. If the angina worsens or acute coronary insufficiency develops, it is recommended that nebivolol be promptly reinstituted, at least temporarily.

Peripheral Vascular Diseases
ß-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular diseases. Caution should be exercised in these patients.

Renal Insufficiency
Nebivolol should be used with caution in patients on dialysis.

Geriatric Patients
In patients above 75 years, caution must be exercised and these patients should be monitored closely.

Others
- Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration. Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.
- Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Pregnancy
Nebivolol should be used during pregnancy (category C) only if the potential benefit justifies the potential risk to the fetus. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn must be closely monitored. Symptoms of hypoglycemia and bradycardia are generally to be expected within the first 3 days.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because of the potential for ß-blockers to produce serious adverse reactions in nursing infants, especially bradycardia. Nebivolol is not recommended during nursing.

Drug Interactions
- Nebivolol should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [*verapamil*] and benzothiazepine [*diltiazem*] classes) or antiarrhythmic agents such as *disopyramide* are used concurrently.
- Both *digitalis glycosides* and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
- Patients receiving catecholamine-depleting drugs such as *reserpine* or *guanethidine* should be closely monitored.
- In patients who are receiving nebivolol and *clonidine*, nebivolol should be discontinued for several days before the gradual tapering of *clonidine*.

CYP2D6 *inhibitors*: Caution should be used when nebivolol is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine etc.)

Cimetidine: Cimetidine causes a 23% increase in the plasma levels of d-nebivolol.

Sildenafil: The co-administration of nebivolol and a sildenafil decreased AUC and C_{max} of sildenafil by 21 and 23% respectively. The effect on the C_{max} and AUC for d-nebivolol was also small (<20%).

OVERDOSE
The most common signs and symptoms associated with nebivolol overdosage are bradycardia and hypotension. Other important adverse events reported with nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β-blocker overdose include bronchospasm and heart block. If overdose occurs, nebivolol should be stopped and general supportive and specific symptomatic treatment should be provided.

AVAILABILITY
Nebivolol (Nebil) Tablets 2.5mg are available in Alu-Alu blister pack of 7's and box of 14's.
Nebivolol (Nebil) Tablets 5mg are available in Alu-Alu blister pack of 7's and box of 14's.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from light and moisture.
The expiration date refers to the product correctly stored at the required conditions.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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